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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Application Number: 09/295,463
Filing Date: April 13, 1999
Appellent(s): COWSERT ET AL.

Paul K. Legaard
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2/14/06 appealing from the Office action

mailed 5/23/05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,463,564	AGRAFIOTIS et al.	10-1995
5,639,603	DOWER et al.	6-1997
5,720,923	HAFF et al.	2-1998

5,650,122   HARRIS et al.   7-1997

UHLMANN et al. "Antisense oligonucleotides: A new therapeutic principle." Chemical

Reviews, vol. 90, no. 4 (June 1990), pages 543-584.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 are again rejected, as

previously set forth in the office action of 6/9/04 and further elucidated in the Advisory

Action of 12/9/04, under 35 U.S.C. 112, first paragraph, as failing to comply with the

written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession

of the claimed invention. This is a NEW MATTER rejection.

The amendment filed 8/4/03 introduces new matter as follows. Amended claim

55 now recites generating virtual compounds according to thermodynamic property "and

at least one criteria selected from...". This limitation wherein said generating is

practiced via the combination of a thermodynamic property "and" the listed properties to

control the generating step in claim 55 has not been found as filed regarding written

basis. Figures 4-6 fail to provide support for the combination of a thermodynamic

property and at least one other criterion in a step of generating in silico compounds. As

the Figures disclose that a step of generating oligonucleotide sequences is performed

BEFORE any step of calculating thermodynamic properties or scores, there is no

support in the Figures for generating an in silico compound of any kind "according to" a

thermodynamic property, whether in combination with another a property or alone. The

method disclosed in the Figures is one wherein a list of PREVIOUSLY GENERATED

compounds is selected based on various properties. This is not reflected in the steps of

the rejected claims. Further, and as previously set forth, the assessment of a

compound for a criterion such as hybridization (targeting) is performed separately from

the thermodynamic property calculations. Figures 5 and 6 present these steps as being

separate, with no overlapping or connecting elements which would lead one skilled in

the art to interpret them as being performed in combination, as embodied by the

limitations of the pending claims. Pages 19-24 of the originally filed specification also fail

to provide support for the limitations in question. Page 19, lines 16-18 discloses that

FOLLOWING calculation of thermodynamic properties, desired sequence properties to

be scored are selected. The disclosure of pages 19-24 contains references to the

Figures. Again, it is noted that all "scoring" is preformed as a selection step AFTER

generation of virtual oligonucleotides, and is not performed as part of the generation

step itself. Further, the criteria listed in the claims for combination with thermodynamic

properties do not coincide with the "sequence properties" or "homology" calculations

disclosed by the specification and Figures as being scored following the thermodynamic

calculations. The above noted NEW MATTER is also present in independent claims

56, 58-60, 62-67, 69-72, 74, 75, 78-82, 85-87, 99-102, as well as claims dependent

directly or indirectly from these independent claims via their dependence.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 are again rejected under

35 U.S.C. 103(a) as being unpatentable over AGRAFIOTIS et al. (5,463,564) in view of

UHLMANN et al. (1990), DOWER et al. (5,639,603), and HAFF et al. (5,720,923) or

HARRIS et al. (5,650,122).

The claims are directed to methods of generating or evaluating in silico

compounds according to a thermodynamic property and at least one other criterion, and

robotically assaying synthetic compounds for one or more desired physical, chemical, or

biological properties. Some methods also include a step of synthesizing at least some

of the virtual compounds before assaying. Claims 58, 60-672, 74-83, 85-87, and 100-

102 limit the compounds to nucleobases or oligonucleotides.

AGRAFIOTIS generically describes computerized design of a directed diversity

chemical library, as well as computer-directed synthesis and testing of designed

compounds for desired properties (abstract and Figure 2). AGRAFIOTIS specifically

teaches that his design, synthesis, and testing are iterative steps, and teaches testing

and evaluation for desired chemical, biological and/or physical properties (col. 3, lines

27- 68). AGRAFIOTIS teaches that his chemical library thus designed may comprise a

variety of different compounds, including drugs and bioactive compounds (col. 5, lines

46-55), and teaches that it is well-known in the art for such libraries to comprise

oligonucleotides as bioactive compounds (col. 2, lines 32-44). AGRAFIOTIS teaches

design/evaluation of his virtual compounds according to various criteria, including

binding to a target (col. 16, line 60-col. 17, line 25), but does not specifically teach

design/evaluation according to the properties recited in the instant claims.

UHLMANN generally teaches methods of design and synthesis of a variety of

drugs, specifically antisense oligonucleotides. Pages 553-556 describe design of

antisense molecules according to thermodynamic and "other criteria" in order to

achieve desired properties. Pages 561-562 teach synthesizing and testing for desired

properties, specifically hybridization/melting temperature (i.e. a thermodynamic

property) and ability to bind to a target. Pages 565-567 disclose other desired

properties, including stability and bioavailability. UHLMANN does not teach computer-

controlled PCR or ELISA.

DOWER teaches automated synthesis and testing of oligonucleotides with

desired properties, specifically those with desired hybridization and receptor binding

properties (col's 16-19).

HAFF teaches automated PCR.

HARRIS teaches automated ELISA.

It would have been obvious to one of ordinary skill in the art at the time of

invention to have used the method of automated design and synthesis of drugs, as

taught by AGRAFIOTIS, to design and synthesize the antisense drugs according to the

thermodynamic and binding parameters taught by UHLMANN, combined with the

synthesis steps taught by DOWER, where the motivation would have been to facilitate

design and testing of new drugs by rational drug design, as taught by UHLMANN as

being desired by those of skill in the art (p. 544). It would further have been obvious to

have assayed the antisense drugs in the method of AGRAFIOTIS, UHLMANN and

DOWER using either the automated PCR or ELISA of HAFF or HARRIS, respectively,

where the motivation would have been to "scale up" the volume of product, as taught by

HAFF (col. 2, lines 20-63), and/or to increase the reliability of results, as taught by

HARRIS (col. 2, lines 35-58). One of skill in the art would reasonably have expected

success in designing, synthesizing and testing the antisense oligonucleotide drugs of

UHLMANN using the combined in silico design and computer-implemented steps of

AGRAFIOTIS, in combination with the computer-implemented assays of HAFF or

HARRIS, because both AGRAFIOTIS and DOWER teach that computer-implemented

design and synthesis of oligonucleotides from combinatorial libraries is known in the art

to have been successful.

(10) Response to Argument

A)   In response to the argument that the method of AGRAFIOTIS **begins** with a

synthesis step followed by a "generation of a virtual library" and thus does not teach

generation or evaluation of in silico or virtual compounds **prior to** synthesis or assay, it

is noted that appellants have, by their own arguments, admitted that AGRAFIOTIS

teaches BOTH in generation of a virtual (or in silico) library and synthesis of

compounds. Appellants argument that these steps are not aught in the exact order of

the claims are not persuasive for the following reasons. First, AGRAFIOTIS does teach

a design step **prior to** a synthesis and/or assay step where he teaches that his method

is reiterative and that steps of computer-controlled evaluation and design (computer-

generation of models/compounds) are followed by synthesis of the designed

compounds (col. 3, line 35-col. 4, line 25). In addition, AGRAFIOTIS explicitly teaches a

"synthesis protocol generator" which incorporates "desired activity properties" BEFORE

"robotics synthesis instructions" occur in Figure 2. Second, the instant claims recite

open claim language, and thus do not exclude additional steps such as those also

taught by AGRAFIOTIS.

In response to the argument that the design (in silico generation or evaluation)

step of AGRAFIOTIS is not carried out "according to" thermodynamic and other criteria,

it is noted that the "synthesis protocol generator" of AGRAFIOTIS uses structural,

electronic, and physiochemical criteria, and **receptor fit criteria** to generate a directed

diversity chemical library (col. 16, lines 42-68), thus AGRAFIOTIS does, in fact, teach

using a variety of criteria to generate/evaluate his computer-designed compounds,

wherein at least on criterion is "targeting to a functional region." It is noted that the

rejection is made over a combination of references, wherein UHLMANN and DOWER

teach design and evaluation of nucleic acids according to thermodynamic (e.g. melting

temperature) and targeting to a functional region of a target nucleic acid (e.g.

hybridization/binding properties) criteria.   Appellant merely argues that the combination

of references does not overcome the "deficiencies" argued for the AGRAFIOTIS

reference, and does not set forth any specific arguments with regard to the combination

of references.

In response to the argument that the "synthesis protocol generator" of

AGRAFIOTIS only directs synthesis of actual compounds, but not in silico compounds,

it is noted that col. 17, lines 6-25 and col. 18, lines 15-40 of AGRAFIOTIS describe

construction of structure-activity models and identification of compounds by the

synthesis protocol generator from those models TO BE synthesized in the next iteration.

Clearly, compounds must be generated in silico in order for filtering and selection of

compounds for FUTURE synthesis to occur.

B)   In response to the argument that Figures 4 and 5 provide support for

""numerous criteria" which can be used to generate in silico compounds, it is noted that

Figure 4 does teach a step (304) of generating all possible oligonucleotides capable of

hybridizing to a target sequence, which in combination with step (305) of generating

virtual oligonucleotides, may be interpreted as providing support for a step of generating

virtual compounds according to a criterion of "targeting to a …target nucleic acid" as

recited in the claims, but this "generation" step is clearly NOT performed "according to"

a thermodynamic property. Figure 4 does not disclose any step of *generation* or

according to a thermodynamic property, but discloses only a step (306) of *calculating*

thermodynamic properties AFTER the generation step. A step of calculating a

thermodynamic property may be interpreted to be a step of evaluating according to that

property, but then the step of "generating" by hybridization is clearly not one of

"evaluating." Step of listing (348) and selecting (349, in Figure 5) are separate steps

following the generation and calculation steps and are not interpreted to be either

generation or evaluation steps. Neither Figure 4 nor Figure 5 discloses ANY step which

includes generating or evaluating an oligonucleotide or any other compound according

to BOTH thermodynamic AND another criterion.

In response to the argument that there is "confusion" between "generating in

silico virtual *compounds*" as recited in claim 55, and "generating oligonucleotide

sequences," it is noted that Figures 4 and 5, and page 16 of the specification, to which

appellants point to support, specifically disclose generating "oligonucleotide

sequences." While the instant specification does provide support for generating

"synthetic compounds" on page 1, the overall disclosure is directed to design and

synthesis of oligonucleotide sequences, thus appellant's attempt to distinguish the

"compounds" of claim 55 from "oligonucleotides" is confusing. Further, claims 58, 60,

62-72, 74-76, 78-83, 85-87, 100-102 specifically recite generating/evaluating

nucleobase or oligonucleotides, therefore the argument is moot with regard to these

claims.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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